REMARKS/ARGUMENTS

The Status of the Claims.

Claims 1-13 are pending with entry of this amendment. Claims 1, 2, 4 and 7 are amended herein. These amendments introduce no new matter and support for the amendments is replete throughout the specification. These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

Claim 1 is amended to remove language that the Examiner interpreted as introducing an unsupported negative limitation to the claim. Furthermore, to clarify the nature of the "cognate receptor," the claim has been amended to explicitly indicate in a manner unambiguously consistent with the specification, that the cognate receptor is a member of the transcription factor superfamily. Support for a cell comprising an estrogen receptor and an additional member of the transcription factor superfamily can be found throughout the specification. For example, see specification at page 3, line 16-17; p. 16, lines 6-21.

Claims 2, 4, and 7 are amended solely to correct inadvertent typographical errors (e.g., omission of the term "cognate" with reference to "a receptor for said nuclear transcription factor ligand") and correct punctuation. Applicants submit that no new matter has been added to the application by way of the above Amendment. Accordingly, entry of the Amendment is respectfully requested.

35 U.S.C. §112, Second Paragraph.

Claims 1-13 were rejected under 35 U.S.C. §112, second paragraph, as indefinite because the metes and bounds of the term "nuclear transcription factor ligand" is alleged to be unclear. In particular, the Examiner alleges that the specification refers to members of the nuclear transcription factor superfamily without providing structural limitation. To the extent the rejection is applied to the amended claims, Applicants traverse.

The nuclear transcription factor superfamily, encompassing the steroid receptors (e.g., estrogen, progestin, androgen, mineralocorticoids, glucocorticoids); retinoic acid receptors; vitamin D receptors; and prostaglandin receptors, among others, is a superfamily of structurally related gene products well known in the art at the filing date of the present application. Indeed, the term superfamily has been used to refer to these structurally related transcription factor receptors since at least as early as 1988 (Evans **1988** Science 240:889-895), and the use has continued through the present day, evidencing its widespread acceptance. Any practitioner of skill in the art would immediately recognize that a nuclear transcription factor ligand, defined as "a compound that binds to a nuclear transcription factor" referred unambiguously to a compound that binds to a protein encoded by the gene superfamily including, e.g., an estrogen receptor, a progestin receptor, an androgen receptor, a mineralocorticoid receptor, a glucocorticoid receptor, a retinoic acid receptor, a vitamin D receptor, a prostaglandin receptor, and structurally related proteins. Those of skill in the art are very familiar with the structural definition of (and identity of more than 150 species comprehended within) the superfamily of nuclear hormone receptors

which act as transcription factors via specific DNA binding interactions. For example, Evans, in 1988 referring to the steroid and thyroid hormone receptors, discusses support for the proposal "that there is a large superfamily of genes whose products are ligand-responsive transcription factors" that possess "a highly conserved DNA sequence element," and provides sequence alignments and schematic comparisons illustrating structurally conserved functional domains shared by members of the superfamily.

More recently, a review authored in 1995 (two years before the priority date of the present application), by prominent researchers from 9 institutions from 4 countries in North America, Europe and Asia, refers to a "single family of receptors for steroids, retinoids, and thyroid hormones." (Mangelsdorf et al. **1995** Cell 83:835-839). This family of molecules "are characterized by a central DNA-binding domain (DBD), which targets the receptor to specific DNA sequences known as hormone response elements. The DBD is composed of two highly conserved zinc fingers that set the nuclear receptors apart from other DNA-binding proteins. The C-terminal half of the receptor encompasses the ligand-binding domain (LBD), which possesses the essential property of hormone recognition and ensures both specificity and selectivity of the physiologic response." This review in the widely read journal Cell, identifies more than 150 mammalian members of the superfamily, as well as numerous invertebrate, e.g., *Drosophila* and *C. elegans*, members of the family by Genbank accession number.

Similarly, a review by Ribeiro et al. (including inventor Kushner) published in 1995 in the widely distributed and read Annual Review of Medicine, commences with the statement: "[t]he nuclear hormone receptor gene superfamily encodes structurally related proteins that regulate transcription of target genes." These authors list as members of the family, the "structurally related" receptors for glucocorticoids, androgens, mineralocorticoids, progestins, estrogens, thyroid hormones, viramin D, retinoic acid, and 9-cis retinoic acid, as well as receptors for other ligands."

Thus, anyone possessing even rudimentary skill in the art, given the disclosure of the present application, e.g., on pages 5 and 6, would immediately recognize that the term "nuclear transcription factor ligand" referred to, and exclusively to, a compound which binds to a member of the aforementioned superfamily. The structural limitations of this superfamily are not only well known and universally accepted in the art, but can if necessary be deduced by a sequence analysis of any number of the family members, e.g., as indicated by the Accession Numbers provided by Mangelsdorf et al.

The claims are also rejected under 35 U.S.C. § 112, second paragraph on the grounds that the metes and bounds of the term "cognate receptor" is allegedly unclear. Again, Applicants traverse. The term "cognate receptor" in reference to a ligand is used in the art in a manner consistent with the explicit definition provided on p. 6, line 13 of the specification. As discussed above, it is evident that the claims read in light of the specification refer to a cognate receptor belonging to the superfamily of transcription factors including the hormone receptors described throughout the specification and discussed herein. Nonetheless, to aid the Examiner's understanding of this element, the language has been amended to explicitly recite that the cell of claim 1 comprises-in addition to an estrogen receptor, fos and jun-"an additional member of the transcription factor superfamily, which member of the nuclear transcription factor superfamily comprises a cognate receptor for said nuclear transcription factor ligand."

For the reasons discussed above, claims 1-13 are definite and the rejection should be withdrawn.

35 U.S.C. §112, First Paragraph.

Claims 1-13 were rejected under 35 U.S.C. §112, first paragraph on the grounds that the specification did not provide written description for a "negative limitation subgeneric claim" reciting a cell "wherein said cognate receptor is a receptor other than the estrogen receptor, AP-1, fos or jun." As a preliminary matter, the language "wherein said cognate receptor is a receptor other than the estrogen receptor, AP-1, fos or jun" was not a negative limitation, nor was it ever intended to be a negative limitation. This language could only be interpreted as a negative limitation if it was examined in isolation without reference to the other elements of the claim. Rather, a careful reading of the entire claim (indeed a reading solely of element a) of claim 1) renders it evident that in a cell also including an estrogen receptor, fos and jun (which together make up AP-1), an additional receptor is expressed, i.e., a cognate receptor for said transcription factor ligand. Nonetheless, since this language was originally introduced solely in a cooperative attempt to aid the Examiner's understanding of the claimed subject matter, it has been removed.

The claim has been amended to indicate that the method of claim involves:

"a) providing a first cell comprising:

an estrogen receptor;

fos;

jun;

an additional member of the nuclear transcription factor superfamily, which member of the nuclear transcription factor superfamily comprises a cognate receptor for said nuclear transcription factor ligand; and,

a promoter comprising an AP-1 site that regulates expression of a first reporter gene..."

Support for a cell comprising a member of the nuclear transcription factor superfamily in addition to an estrogen receptor, fos and jun is found throughout the specification, as indicated above, and the rejection should be withdrawn.

Claims 1-5 and 8-11 were also rejected under 35 U.S.C. § 112, first paragraph on the grounds that the specification allegedly does not provide adequate written description for the term "cognate receptor." Applicants traverse.

As discussed in detail above and explicitly recited in the claims as amended, the cognate receptor is 1) a member of the transcription factor superfamily; and, 2) typically bound by said transcription factor ligand. It is apparent to those of skill in the art that numerous known proteins, i.e., steroid receptors, thyroid hormone receptors, retinoic acid receptors, vitamin D receptors, prostaglandin receptors, and the like, all of which share defined structural features that have been well known at the level of both primary sequence and three dimensional structure since prior to the filing date of the present application, not only provide "the metes and bounds" of this element of the invention, but also supply comprehensive written description of the claimed invention. The fact that the sequences themselves are omitted from the application is irrelevant. Any practitioner of even minimal familiarity with the relevant art is not only conversant with the superfamily of receptors, including, e.g., the steroid receptors, the thyroid hormone receptors, etc., but can quickly and

comprehensively ascertain the primary amino acid and nucleotide sequence of numerous known members of the family, e.g., based on accession numbers published in the prior art at the time the application was filed as well as using search engines, such as BLAST and entering even a single member of the superfamily (such as, for example, an estrogen receptor, a thyroid hormone receptor, an androgen receptor, etc.). While it is (and was at the time the application was filed) a trivial matter, for one familiar with the art to obtain such publicly accessible sequences by querying with a sequence, it is equally simple to query a sequence database such as Genbank, using the "functional" name of the protein, e.g., estrogen receptor, thyroid hormone receptor, retinoic acid receptor, etc., to obtain the primary sequence of that protein as well as numerous related proteins.

Given the widespread accessibility of such publicly available structural definitions of the claimed subject matter, and the simplicity with which such information is obtainable by those of skill in the art, it is simply improper to maintain a rejection on the grounds that the specification fails to provide a structure for the term "cognate receptor" which obviously can clearly be envisioned by one skilled in the art.

Additionally, claims 1-13 were rejected under 35 U.S.C. § 112, first paragraph, apparently on the grounds that the method includes non-functional species of estrogen and cognate receptors. Applicants traverse.

Claims are not overbroad "just because they read on even a very large number of inoperative embodiments." *In re Cook and Marigold*, 169 USPQ 298 (CCPA 1971). "For a proposed claim to be unpatentable, the law requires that the number of inoperable embodiments be significant in numbers *and not readily ascertained by those of skill. Id.* at 301-302. (emphasis added).

The methods of claims 1-13 are methods for "screening a nuclear transcription factor ligand for the ability to modulate estrogen activation at an AP-1 site..." That is, the claims are drawn to methods of identifying nuclear transcription factor ligands with a particular effect (i.e., the ability to modulate estrogen activation at an AP-1 site) from nuclear transcription factor ligands without the specified effect.

This rejection appears to be based on the existence of 1) orphan receptors, and/or 2) variants of receptors which bind a known ligand, which may due to an unspecified mutation be non-functional. Firstly, the term "orphan receptor" does not indicate that the receptor in question is non-functional. "The term orphan receptor was coined in the late 1980's to describe the first of what has become a large number of novel gene products that by homology belong to the nuclear receptor superfamily, but for which ligands are initially unknown." (*see*, Mangelsdorf and Evans **1995** Cell 83:841-850). With respect to any particular protein which by sequence is known to be a member of the nuclear transcription factor superfamily, at the time of its identification, i.e., cloning and sequencing, its ligand may be unknown, and it will, therefore, be classified as an orphan receptor. Upon identification of the cognate ligand, the same molecule loses the designation of "orphan receptor" and is designated in accordance with its now recognized binding properties. This schema for the identification and nomenclature of members of the nuclear transcription factor superfamily is well established, and understood by those of skill in the art. Indeed, as the so-called orphan receptors are typically isolated from cDNA and genomic libraries, there is no preconception in the art that such molecules are non-functional in nature.

Secondly, the potential existence of natural or synthetic variants of receptors with known function, in no way renders the specification non-enabling for claims 1-13. As stated by the PTO Board of Appeals: "[i]t is always possible to theorize some combination of circumstances which would render a claimed composition or method inoperative, but the art-skilled would assuredly not choose such a combination. *Ex parte Cole*, 223 USPQ 94 (BPIA 1983). Numerous functional species meeting the limitations of the claims are known to those of skill in the art. The mere fact that a practitioner could obtain one, or even many, non-functional variants of such receptors is simply irrelevant to the practice of the claimed method. Rather, the relevant inquiry is whether one of skill would be able to ascertain whether an embodiment was operative or inoperative. With respect to the claimed invention, one of skill in the art would recognize that in order to evaluate a functional attribute, e.g., the ability of a nuclear transcription factor to modulate an estrogen response via its cognate receptor, a functional cognate receptor (of which more than 150 are known in the art) should be selected. Indeed, it would be immediately apparent to one of skill in the art that selection of a non-functional cognate receptor would not be desirable. Furthermore, since the amino acid sequences of numerous exemplary functional cognate receptors are publicly available, it would be a trivial matter to avoid selection and utilization of non-functional variants thereof.

Thus, the full scope of claims 1-13 is enabled by the teachings of the specification, and the rejection should be withdrawn.

35 U.S.C. §103(a).

Claims 1-13 were rejected under 35 U.S.C. §103(a) as allegedly obvious in light of Kushner et al., USPN 5,723,291 (the " '291 patent") in view of Pfahl et al. (6,004,748); Evans et al. (USPN 5,639,592); Gaub et al. **1990** Cell; Webb et al.; and Kushner WO 95/06754.

Applicants have previously stated that the '291 patent is not prior art under 103(c) because the present application and USPN 5,723,291 were commonly owned or subject to an obligation of assignment to the same person, i.e., the Regents of the University of California.

The Examiner alleges, without providing any corroborating evidence, that the present invention is "owned by both Karo and University of California. Thus it does not meet the common ownership defined in MPEP 706.02(l)(2) because it is not 100% owned."

This allegation is factually incorrect. The present invention was at the time the invention was made (the only relevant requirement of 35 U.S.C. §103(c)) subject to an obligation of assignment solely to the Regents of the University of California, and the present invention is even now assigned solely to the Regents of the University of California, i.e., is 100% owned by the Regents of the University of California, as evidenced by the assignment filed on September 4, 1998, and recorded in the United States Patent and Trademark Office at Reel/frame 9429/0531 on September 8, 1998. The invention was, at one time, licensed to KaroBio. As stated in MPEP 706.02(l)(2) "[a] license of the claimed invention to another by the owner where basic ownership rights are retained would not defeat ownership.

Accordingly, it is entirely clear that United States Patent Number 5,723,291 is not prior art under 103(c).

Obviousness type Double Patenting

Claims 8 was rejected under 37 CFR 1.75 as a substantial duplicate of claim 9. Claim 8 is drawn to a method as recited in claim 1, "wherein said first cell expresses said estrogen receptor from a heterologous DNA. In contrast, claim 9 is drawn to a method as recited in claim 1, "wherein said first cell expresses said cognate receptor from a heterologous DNA." Since the estrogen receptor and the cognate receptor are two distinct elements of claim 1, the fact that either the estrogen receptor or the cognate receptor may be expressed from a heterologous DNA is independent of whether the other of these two recited elements may also be expressed from a heterologous DNA. Thus, claims 8 and 9 are NOT substantial duplicates of each other and the objection should be withdrawn.

Claims 1-13 were also rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-27 of the '291 patent in light of Pfahl, Evans, Gaub, Webb and Kushner as indicated above. An obviousness type double patenting rejection is appropriate if the claimed invention while not identical is not patentably distinct with respect to the claims of a prior patent in light of the prior art. A claimed invention is not patentably distinct if *all of the claimed elements are found* in one or more pieces of prior art, and if there is motivation to combine the prior art with a reasonable expectation of success.

Claims 1-13 of the present invention relate to a method of screening a nuclear transcription factor ligand for the ability to modulate estrogen activation at an AP-1 site. The elements of the method are:

a) providing a first cell comprising:
an estrogen receptor;
fos;
jun;
an additional member of the nuclear transcription factor superfamily,
which member of the nuclear transcription factor superfamily comprises a cognate receptor for said nuclear transcription factor ligand; and,
a promoter comprising an AP-1 site that regulates expression of a first reporter gene;...

The '291 patent relates to a method for screening a test compound involving providing a cell comprising: AP-1 proteins (e.g., fos and/or jun); an estrogen receptor; and, a construct comprising an AP1 site which regulates expression of a reporter gene. None of the claims of the '291 patent recites a member of the nuclear transcription factor superfamily *in addition to* the estrogen receptor and AP-1 proteins, as is found in claims 1-13 of the present invention.

The Examiner has pointed to nothing in any of the cited art which provides the element of an additional member of the nuclear transcription factor superfamily in a cell comprising the other elements of the present invention. Pfahl relates to a method involving binding AP-1 or a component of AP-1 with a nuclear receptor, to inhibit the binding of AP-1 to a gene. Evans relates to a method of identifying a compound in a system including: a cell line that expresses: a steroid hormone receptor, AP-1 and an AP-1 responsive reporter. Similarly, Webb describes an assay system including a cell expressing an estrogen receptor, AP-1 proteins (fos and jun) and a reporter including an AP-1 site. Finally, Gaub et al. allege a system in which an ERE (estrogen response element) is activated in a cell comprising an estrogen receptor and AP-1 proteins. The Examiner has pointed to nothing in any of cited

references which discloses as a further element (i.e., in addition to an estrogen receptor, AP-1 proteins and an AP-1 responsive reporter construct) an additional member of the nuclear transcription factor superfamily.

Thus, the cited art in any combination fails to disclose all of the elements of the invention of claims 1-13, and cannot render claims 1-13 unpatentable. The rejection should, therefore, be withdrawn.

Appended Declaration

The declaration of Dr. Thomas Scanlan addressing certain factual issues discussed herein is appended herewith.

CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, a telephone interview with the Examiner is hereby requested. Please telephone the undersigned at (510) 337-7871 to schedule an interview.

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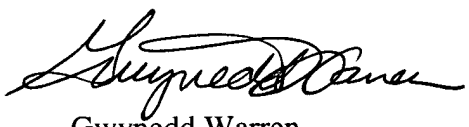
Respectfully submitted,



Gwynedd Warren
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Attachments:

1) A petition to extend the period of response for **1** month;
2) A transmittal sheet;
3) A fee transmittal sheet;
4) A request for continuing examination (RCE);
5) A declaration by Professor Thomas Scanlan; and,
6) A receipt indication postcard.